

Vegetarian dietary patterns and the risk of breast cancer in a low-risk population

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Abstract

Among cancers in American women, breast cancer (BC) has the second highest incidence and mortality. The association of BC with diet has been inconsistent. Studies that evaluate associations with dietary patterns are less common and reflect an individual's whole diet. We associated dietary patterns with the risk of BC in American women of the Adventist Health Study-2 (AHS-2), a prospective cohort of 96 001 subjects recruited between 2002 and 2007. Answers to a previously validated FFQ were used to classify subjects to vegan, lacto-ovo-vegetarian, pesco-vegetarian, semi-vegetarian and non-vegetarian dietary patterns. Incident BC were identified by matching AHS-2 subjects to data from forty-eight state cancer registries. Statistical analyses used proportional hazard regression analyses with covariates that were chosen *a priori*. From 50 404 female participants (26 193 vegetarians), we identified 892 incident BC cases, with 478 cases among vegetarians. As compared with non-vegetarians, all vegetarians combined did not have a significantly lower risk (hazard ratio (HR) 0.97; CI 0.84, 1.11; $P=0.64$). However, vegans showed consistently lower (but non-significant) point estimates when compared with non-vegetarians (all cases: HR 0.78; CI 0.58, 1.05; $P=0.09$). In summary, participants in this cohort who follow a vegetarian dietary pattern did not experience a lower risk of BC as compared with non-vegetarians, although lower risk in vegans is possible. These findings add to the very limited literature associating vegetarian diets with BC risk and can assist nutritionists when evaluating the impact of these diets. The findings will also motivate further evaluation of vegan diets and their special characteristics.

Key words: Breast cancer: Dietary patterns: Vegetarians: Adventists

Breast cancer (BC) is the most common cancer in women across both developed and developing economies⁽¹⁾, and this is true among American women (excluding non-melanoma skin cancers), in whom it is also the second leading cause of cancer death⁽²⁾. Potentially modifiable risk factors include breast density⁽³⁾, body weight, smoking⁽⁴⁾, alcohol consumption⁽⁵⁾, physical activity⁽⁶⁾, radiation exposure⁽⁷⁾, hormone replacement therapy⁽⁸⁾, the use of oral contraceptives⁽⁹⁾ and possibly diet.

It is estimated that a third of cancers could be prevented by diet alone⁽¹⁰⁾, but research findings for BC have not been consistent^(11,12). Countries with high soya intake have a lower incidence of BC⁽¹³⁾. In some studies⁽¹⁴⁾, this protection is lost after migration to lower soya-consuming societies, providing some support for a hypothesis that dietary soya protects against BC. Micronutrients found in fruits and vegetables have also shown protective associations in some reports^(15–20). Associations of dietary fats with BC have also been inconsistent in the literature, although results for SFA often tend towards an increased risk^(21–27). Possible confounding by smoking habits and especially alcohol intake is of concern in some of these studies. The *Continuous Update Project Report* from the

World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR)⁽¹²⁾ lists only total fat in postmenopausal women as having limited but suggestive evidence for causality and that the evidence for other dietary factors in either pre- or postmenopausal women is limited and inconclusive.

Individual foods such as fruits or vegetables, or nutrients, account for only a part of a diet. Studies that evaluate effects of whole diets by focusing on dietary patterns are less common, but they have suggested protective effects for BC from 'Mediterranean' diets, or 'prudent' diets that emphasise vegetables^(28–34). However, definitions of these patterns often include or overlap with vegetarian dietary patterns, and, confusingly, patterns with the same label may be defined differently in different studies, although they have some common features.

There is a paucity of available evidence concerning the effects of vegetarian dietary patterns on risk of BC^(35–37), and again definitions may differ between studies. In an earlier study of California Adventists that included many vegetarians, no strong dietary associations with BC could be identified, although there was some limited evidence of hazard associated

Abbreviations: AHS-2, Adventist Health Study-2; BC, breast cancer; ER, oestrogen receptor; HR, hazard ratio; PR, progesterone receptor.

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with higher cheese consumption⁽³⁸⁾. Similarly, more recent work from EPIC-Oxford did not detect associations, although their vegan participants were proportionately few⁽³⁹⁾.

Here, we analyse associations between vegetarian dietary patterns and BC in women participating in the Adventist Health Study-2 (AHS-2), which has rates of BC that are >20% lower than usual⁽⁴⁰⁾, very low rates of tobacco and alcohol consumption, a wide diversity of dietary habits and overall good health. Diet is classified into five patterns (vegan, lacto-ovo-vegetarian, pesco-vegetarian, semi-vegetarian and non-vegetarian). Our *a priori* hypothesis is that risk of BC will be lower in the vegetarian (especially vegan, lacto-ovo- and pesco-vegetarian) groups than in the non-vegetarians.

Methods

Ethics statement

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Institutional Review Board of Loma Linda University. Written informed consent was obtained from all subjects.

Study design and population

The AHS-2 is a prospective cohort of 96 001 subjects in the USA and Canada that was designed to study associations between lifestyle and cancer risks. Subjects were recruited and enrolled with the completion of the baseline questionnaire between 2002 and 2007, hence providing dietary information at that time. The cohort includes 62 511 women (17 952 female black subjects of American or Caribbean descent) and has been described previously⁽⁴¹⁾. Mean follow-up time was 7.8 years.

Here we include participants from forty-eight states and Washington, DC, where matching with cancer registries had been completed; thus, we include cases diagnosed by the end of 2011 for thirty-three registries (including DC), 2010 for an additional ten states, 2009 for three states and 2008 for the remaining two states. We excluded Canadian participants (as vital status had not been established for all), also those with a prevalent cancer, age < 35 years, participants with questionnaires having more than seventy FFQ missing or kJ/kcal intake < 500 or > 4500, as well as also women who reported never having had a menstrual period. Thus, 50 404 women were finally included in the analysis.

Dietary assessment and cancer ascertainment

Dietary patterns were determined according to the intake frequency (thinking over the past 1 year) of specific foods (red meat, poultry, fish, eggs and dairy products) using a previously validated FFQ. The validation was against six 24-h dietary recalls in a calibration sub-study. The validity correlations for foods of relevance here for non-black subjects are red meat (0.76); poultry (0.76); fish (0.53); dairy protein and fat (0.77, 0.66); and eggs (0.64). Similar results for Black subjects are 0.72; 0.77; 0.57; 0.58, 0.56; and 0.52^(42,43).

Categories of intake frequency on the FFQ ranged from 'never or rarely' to '> 2 times/d' for the meat groups, or to '> 6 times/d' for the dairy group. Meats included red meats (beef, lamb), poultry (chicken, turkey) and fish (salmon, white fish, tuna, other fish). Dairy variables included low-fat or regular milk and its derivatives (cheese, cottage cheese, butter, yogurt, ice cream and so on). There were three possible serving sizes: a supplied standard, 'half or less' and 'half or more' of this standard.

Subjects were classified as 'vegan' if their intake of egg, dairy or meat products was less than once per month; as 'lacto-ovo-vegetarians' if their intake of fish, poultry and red meats was less than once per month and their intake of eggs or dairy products was more than or equal to once per month; as 'pesco-vegetarian' if fish intake was ≥ 1 times/month, while red meats and poultry were consumed less than once per month, but no constraints on dairy products or eggs; as 'semi-vegetarians' if intake of red meats, poultry or fish, but not only fish was more than or equal to once per month but less than once per week; and as 'non-vegetarians' if intake of red meat, poultry or fish (but not only fish) was more than or equal to once per week. A dichotomous 'vegetarian' variable that combined vegans, lacto-, pesco- and semi-vegetarians was used for comparison with non-vegetarians to preserve adequate numbers in some analyses.

As described elsewhere in detail^(44,45), these dietary categories differ in major ways by their intake of different foods and nutrients. The more vegetarian categories have profiles generally thought to be more healthy (greater intakes of carotenoids, folate, isoflavones, α -linolenic acid, fibre, Mg, K, fruits, vegetables, nuts, legumes, soya foods, as well as the lesser intakes of animal products). The meat intakes of the non-vegetarian group in AHS-2 are lower than those in the general population, with mean intakes of about 18 g/d of red meats, 22 g/d of poultry and 19 g/d of fish⁽⁴⁵⁾.

Cancers were mainly identified by linkage to cancer registries. An AHS-2 programmer performed the match where possible, and in other situations he was usually online with the registry staff during the match. The AHS-2 programmer used Registry Plus™ Link Plus⁽⁴⁶⁾ matching software, and this was often also used in the other matches. The software provides a score that was used to categorise potential matches as definite non-matches, definite matches and a remaining inconclusive category. Most of the inconclusive matches were resolved by the computer application of matching codes based on twelve matching variables. These had been developed by consensus to further identify matches and non-matches. A much smaller inconclusive zone remained that was resolved by manual review, usually in collaboration with registry staff.

As a backup, biennial hospitalisation history forms (completed by 75% of subjects) included questions about recent hospitalisations and cancer diagnoses. Additional incident cases from this source (finally constituting about 2% of the total) were validated first by phone calls to the subjects, and those not excluded were finally verified by obtaining medical records⁽⁴⁷⁾. Our diagnostic information contained hormone receptor status for 82% of BC cases.

Covariates

Covariate data were collected at enrolment to AHS-2 in the baseline questionnaire. We selected potential covariates to include established or suspected non-dietary risk factors. Less established risk factors^(4,5,48–50) were retained in the model if they changed the β -coefficients of interest by at least 10%. Race was self-defined by participants (Black if participants self-identified as African-American, West-Indian/Caribbean, African or other Black and non-Black otherwise). In regression analyses, BMI was modelled as underweight (<18.5 kg/m²), normal weight as a reference (18.5–24.99 kg/m²), overweight (25–29.99 kg/m²) and three degrees of obesity (1°: 30–34.99, 2°: 35–39.99, 3°: \geq 40). Product terms were also included between BMI categories and menopausal status to allow the BMI effect to depend on menopausal status. Height in inches is reported as a continuous variable. Breastfeeding was a continuous variable corresponding to the sum of breastfeeding months as reported by participants. Physical activity was reported in minutes per week of vigorous activities (brisk walking, jogging, bicycling and so on). Family history of cancer was considered to be positive when BC or ovarian cancer was reported in paternal or maternal first-degree relatives and/or siblings. Our BC screening variable identifies subjects who enrolled after the age of 42 years and reported mammography during the previous 2 years. Participants who had reported a complete cessation of their natural periods because of natural causes, radiation, chemotherapy, bilateral oophorectomy, hysterectomy after the age of 55 years (the 90th percentile of natural age at menopause), as well as all participants 60 years or older at baseline, were considered menopausal. In addition, women <60 years of age (or <56 years for those post-hysterectomy) whose 'doctors considered them to be perimenopausal' were counted as menopausal. However, their age at menopause was calculated as age at enrolment plus 2 years, considering that 4 years is a common duration for perimenopausal status⁽⁵¹⁾. For others, age at menopause was defined as the reported age at menopause for menopausal women or age at bilateral oophorectomy in the absence of oral contraceptive therapy. Age at birth of the first child was classified as either those who had their first birth before age 30 years or those that were either nulliparous or gave birth after the age of 30 years. The use of birth control pills was scored as ever or never. Hormone replacement therapy was assigned as oestrogen or progesterone therapy for purposes other than contraception. Hormone replacement therapy was considered relevant if it lasted >1 year and was used within 5 years of enrolment. Smoking was entered as a binary variable for lifetime use (ever/never). Alcohol was considered positive in those who reported any consumption at enrolment or within the previous 2 years.

Educational status was coded in three levels: grade school, trade school or high school diploma; some college education; and college degree or higher. This variable is used as a surrogate for socio-economic class.

Statistical methods

Attained age was the time variable used in the proportional hazards regression analyses. The models were left-censored at

age of entry to the study. Right censoring occurred at the first date of any of the following: BC diagnosis, death, loss to follow-up or the last date of follow-up. The latest year-end for which a subject's home-state cancer registry had complete data when we matched was the date of last follow-up for subjects not previously satisfying other censoring criteria. The statistical model included four indicator variables for the five dietary patterns (non-vegetarian was the reference pattern), as well as a race variable (1 = Black), and other covariates as indicated in footnotes.

Some variables were relevant only when nested within a population sub-group. In regression models, variables indicating the subgroup (e.g. menopausal/non-menopausal women) were included as main effects along with products between these and the relevant nested exposures of interest (e.g. hormone replacement therapy).

Because BMI may be an intermediary between diet and cancer, models are reported with and without BMI as a covariate. Cancers were coded, where the data were available, as oestrogen or progesterone receptor (ER/PR) positive or negative. Competing risk analysis⁽⁵²⁾ was used to measure the risk of the different cancer subgroups (ER/PR status).

Missing data were handled through multiple imputation (five data sets with imputed missing data) using the Hmisc package in the R language conditional on all variables included in the Cox model. This uses predictive mean matching, and on inspection it produced frequencies of vegetarian patterns (where there had been missing data) similar to those of other subjects. Variances of β -coefficients were estimated using all imputed data sets⁽⁵³⁾. Missing dietary data were imputed at the level of individual FFQ (between 3 and 8% missing for particular questions), and could usually be guided by results from a random subset of missing data for the same variables that had been filled-in by telephone contact⁽⁵⁴⁾. Dietary patterns were then assigned using the imputed data sets.

Results

During the 393 554 person-years of follow-up (average of 7.8 years/person), we identified 892 cases of BC: 414 cases in the non-vegetarian group and 478 cases in vegetarians. Age at enrolment ranged from 35 to 110 years in the full cohort, whereas for BC cases age at enrolment ranged from 35 to 100 years.

Age and race-standardised means, or proportions, for variables of interest, stratified by dietary category, are shown in Table 1. Approximately half of the cohort was non-vegetarian. Compared with participants with other dietary patterns, they had lower educational attainment, an earlier age at first childbirth and lower age at menopause.

They had the highest BMI values, and the highest proportions that used oral birth control pills, or had a positive family history of cancer, but the lowest levels of physical activity. In contrast, vegans had a much lower mean BMI, had the lowest rates of hormone replacement therapy, lowest use of oral birth control pills, the lowest parity, as well as the least compliance with recommendations for cancer screening, but the highest levels of

Table 1. Distribution of participants, dietary patterns and covariates by case/non-case status

	Non-cases	Cases	P
Dietary pattern (age-standardised to full cohort)			
Vegetarian	51.9%	53.1%	<0.0001
Vegan	7.5%	5.5%	<0.0001
Lacto-ovo-vegetarian	28.4%	31.3%	<0.0001
Pescetarian	10.3%	10.2%	0.23
Semi-vegetarian	5.8%	6.1%	0.0009
Non-vegetarian	48.1%	46.9%	<0.0001
All subjects	49 512	892	NA
Covariates (age-standardised to full cohort)			
Age at censoring (years) (mean)	64.77	61.82	<0.0001
Age at menarche (years) (mean)	12.54	12.35	0.0003
Age at first birth (years) (mean)	24.04	24.44	0.051
Age at natural menopause (years) (mean)	47.85	48.67	0.0008
BMI (kg/m ²) (mean)	27.38	27.58	0.37
Height (inches) (mean)	64.24	64.39	0.16
Menopause (%)	69.0%	69.0%	0.60
Hormone replacement therapy (% among menopausal women)	37.7%	43.6%	<0.0001
Oral birth control (%)	60.0%	61.5%	<0.0001
Family history of breast cancer (%)	11.7%	22.1%	<0.0001
Family history of ovarian cancer (%)	4.1%	4.0%	0.51
Family history of breast or ovarian cancer (%)	15.0%	25.2%	<0.0001
Parity (% at baseline)	84.3%	84.1%	0.051
Breastfeeding (total months) (mean)	12.26	11.55	0.16
Number of children	2.71	2.60	0.018
Some college or higher	78.3%	78.1%	0.25
Screening (% of mammography last 2 years)	71.8%	77.1%	<0.0001
Physical activity (min/week)	74.43	75.75	0.71
Smoking (% ever)	16.2%	14.1%	<0.0001
Alcohol (within 2 years of enrolment)	10.9%	12.6%	<0.0001

physical activity. Table 2 summarises hazard ratios (HR) from proportional hazards models, with covariates chosen as described above. There was no evidence of a different risk for BC in vegetarians compared with non-vegetarians. This was true in both pre- and postmenopausal women, although CI were wide in the first group.

However, the point estimate for vegans suggested the possibility of lower risk in this group (HR 0.78; 95% CI 0.58, 1.05; $P=0.09$), although this fell short of statistical significance particularly if one takes account of the multiple testing among the vegetarian categories. Adding BMI to the model shifted the point estimate towards the null (HR 0.84; 95% CI 0.62, 1.13; $P=0.25$) – the change in point estimate suggesting some mediation of any vegan dietary effect by BMI. Changing the reference group to include also pesco- and semi-vegetarians did not substantially alter these results.

Table 3 presents HR analysed by race. As in the previous analyses, there was no evidence that vegetarians were protected overall. Again vegans had the lowest risk in each racial group, but without statistical significance.

Results stratified by hormone receptor status (ER+/PR+; ER-/PR-; *ER+/PR-) are not shown in detail. With the exception of ER+/PR+, numbers are small resulting in inadequate power. For the ER+/PR+ cancers there was no convincing evidence of any association with the vegetarian categories.

Certain covariates were also independently associated with BC risk (not shown in the tables). An earlier age at menarche (menarche before age 14 years) was associated with an increase of risk (HR 1.19; 95% CI 1.01, 1.42; $P=0.043$). Family history of

BC was associated with an almost 2-fold increase in risk when compared with others (HR 1.91; 95% CI 1.63, 2.24; $P<0.001$). Within the ages often associated with perimenopausal years, a woman who was already menopausal was at a lower risk than a woman who was still premenopausal (HR 0.51; 95% CI 0.29, 0.91; $P=0.024$). Appropriate screening was possibly associated with higher risk (HR 1.172; 95% CI 0.99, 1.39; $P=0.067$).

Discussion

Key findings

The main result is that in this study there was no convincing evidence that vegetarians as a group had lower risk of BC than non-vegetarians either in pre- or postmenopausal, or in Black or White, women. The CI for the total group were relatively narrow, although a small protective effect of vegetarianism could not be excluded. This is in agreement with the findings of the EPIC-Oxford Study, another cohort containing many vegetarians⁽⁵⁵⁾. Nevertheless, it is of some interest that in AHS-2 the vegan diet had a stronger and more consistent negative association with risk of BC than other dietary groups. The estimated relative risks in comparison with non-vegetarians were between 0.70 and 0.82 in different subgroups. These included pre- and postmenopausal women, Black women and those with ER+/PR+ cancers. However, in none of these groups could chance be excluded as an explanation, and the numbers of cases were often small. BMI is considerably lower in vegans, and as a mediating variable this could explain a part of any underlying effect. As far as we know, this is the largest

Table 2. Dietary pattern and breast cancer incidence* (Hazard ratios (HR) and 95% confidence intervals)

	Participants	Cases	No BMI			With BMI		
			HR	95% CI	P	HR†	95% CI	P
Total‡								
Non-vegetarian	24 211	414	1.00	Ref.		1.00	Ref.	
Vegan	3748	52	0.78	0.58, 1.05	0.09	0.84	0.62, 1.13	0.25
Lacto	14 336	289	1.05	0.89, 1.23	0.57	1.08	0.92, 1.27	0.34
Pesco	5179	88	0.91	0.71, 1.17	0.48	0.94	0.73, 1.21	0.65
Semi	2930	49	0.91	0.67, 1.23	0.52	0.91	0.68, 1.24	0.56
All vegetarians	26 193	478	0.97	0.84, 1.11	0.64	1.00	0.87, 1.16	0.97
Postmenopausal								
Non-vegetarian	16 215	333	1.00	Ref.		1.00	Ref.	
Vegan	2700	44	0.77	0.55, 1.06	0.11	0.83	0.60, 1.16	0.27
Lacto	10 096	248	1.06	0.89, 1.26	0.53	1.10	0.92, 1.31	0.31
Pesco	3648	69	0.85	0.64, 1.13	0.25	0.88	0.66, 1.18	0.37
Semi	2148	34	0.73	0.53, 1.06	0.10	0.74	0.52, 1.06	0.10
All vegetarians	18 592	395	0.94	0.80, 1.09	0.40	0.97	0.83, 1.14	0.73
Premenopausal§								
Non-vegetarian	7996	81	1.00	Ref.		1.00	Ref.	
Vegan	1048	8	0.81	0.38, 1.70	0.58	0.86	0.40, 1.82	0.69
Lacto	4240	41	0.96	0.63, 1.45	0.84	0.98	0.64, 1.48	0.91
Pesco	1531	19	1.25	0.75, 2.10	0.40	1.27	0.75, 2.14	0.38
Semi	782	15	1.96	1.12, 3.43	0.019	1.95	1.11, 3.42	0.020
All vegetarians	7601	83	1.12	0.80, 1.57	0.52	1.14	0.81, 1.61	0.44

Ref., referent values.

* Time variable: attained age. Reference group: non-vegetarians.

† For total cases the product menopausal status × BMI was used to allow a different BMI association conditional on menopausal status.

‡ Adjusted for: race, height, physical activity, family history of cancer, mammography in the last 2 years after age 42 years, age at menopause, age at menarche, birth control pills, hormone replacement therapy, age at first child, number of children, breastfeeding, educational level, smoking, alcohol, BMI (as indicated).

§ Adjusted as for the total group but excluding age at menopause and hormone replacement therapy.

Table 3. Dietary pattern and breast cancer incidence by race* (Hazard ratios (HR) and 95% confidence intervals)

	Participants	Cases	No BMI			With BMI		
			HR	95% CI	P	HR	95% CI	P
Non-black								
Non-vegetarian	14 957	291	1.00	Ref.		1.00	Ref.	
Vegan	2888	43	0.80	0.58, 1.12	0.19	0.86	0.62, 1.21	0.39
Lacto	12 331	250	1.00	0.84, 1.19	0.99	1.02	0.85, 1.23	0.80
Pesco	3063	61	0.91	0.68, 1.23	0.55	0.94	0.70, 1.26	0.67
Semi	2354	39	0.83	0.59, 1.17	0.28	0.83	0.59, 1.18	0.30
All vegetarians	20 636	393	0.94	0.80, 1.10	0.45	0.97	0.82, 1.14	0.68
Total	35 593	684						
Black								
Non-vegetarian	9254	123	1.00	Ref.		1.00	Ref.	
Vegan	860	9	0.70	0.35, 1.38	0.30	0.77	0.39, 1.55	0.46
Lacto	2005	39	1.31	0.90, 1.90	0.16	1.39	0.95, 2.05	0.09
Pesco	2116	27	0.94	0.60, 1.48	0.80	1.00	0.63, 1.58	0.99
Semi	576	10	1.25	0.64, 2.43	0.51	1.29	0.66, 2.51	0.46
All vegetarians	5557	85	1.08	0.80, 1.45	0.62	1.15	0.85, 1.56	0.37
Total	14 811	208						

Ref., referent values.

* Time variable: attained age. Reference group: non-vegetarians. Adjusted for: height, physical activity, family history of cancer, mammography in the last 2 years after age 42 years, age at menopause, age at menarche, birth control pills, hormone replacement therapy, age at first child, number of children, breastfeeding, educational level, smoking, alcohol, and BMI × menopausal status (as indicated).

available single study of BC risk among different types of vegetarian women, and the possibility of lower rates in vegans is of some interest. Previously⁽⁴⁷⁾, we had noted that vegans in AHS-2 had a tendency to lower incidence rates of female cancers in general (HR 0.71; 95% CI 0.50, 1.01).

Although the evidence for the association between diet and BC is currently limited⁽¹²⁾, many studies have found a reduction of risk when there is a higher intake of fruit and vegetables^(28,31,32,34,36). This is particularly so for postmenopausal BC^(29,31,32,34,56), which may have stronger links to lifestyle and

environmental factors than premenopausal cancer^(57,58). Contrary to this opinion, however, an analysis in American Black women found stronger associations of a prudent dietary pattern with premenopausal BC. The few reports associating diet with particular hormone receptor variants of BC have often found greater protective associations of fruit and vegetables for risk of ER- BC^(28–30,32,56). The association of red meat, poultry, fish, dairy and soya consumption with risk of BC has been less consistent^(36,37,55,59,60).

Reported associations between specific dietary patterns having some overlap with vegetarianism and BC are relatively few. Although several such studies suggest a protective effect^(28–34,56,59), the WCRF/AICR report considers the evidence inconclusive⁽¹²⁾. This may be in part because dietary patterns that share similar names sometimes have different definitions (e.g. 'prudent', 'healthy' and 'Western' dietary patterns), thus limiting the interpretation of results across studies.

We have reported previously^(44,45) that, compared with the other dietary patterns in AHS-2, vegans are more physically active and have lower intake of energy-dense nutrients, lower Na intake, the lowest intakes of animal and dairy proteins, but a higher intake of foods that are rich in fibre, vitamins and plant-based proteins (e.g. fruits, vegetables, whole grains, nuts, soya). They also have a lesser history of alcohol use. These characteristics satisfy most of the American Cancer Society guidelines and the WCRF/AICR recommendations for the prevention of cancer. Catsburg *et al.*⁽⁶¹⁾, found that subjects meeting all *v.* only one of these criteria experienced a 31% lower BC risk. Their analysis suggested a 4–6% lower risk for each additional recommendation that was met.

Several possibly protective mechanisms against cancer can be identified that are associated with the higher consumption of fruit, vegetables^(47,62–65) and soya^(13,66) and a lower BMI, characteristics typical of most vegans in this population. Higher intakes of non-essential amino acids, characteristic of vegan diets, regulate the insulin-glucagon axis^(67–69), and there are metabolic effects that include greater tissue sensitivity to insulin, and also decreased hepatic production and serum levels of insulin-like growth factor-1. Fruits and vegetables may provide an antioxidant environment, cell membrane protection, reduction and scavenging of nitrite and free-radical blocking⁽⁶⁴⁾. These properties can potentially influence cancer progression and development through inhibition of metastasis, induction of apoptosis, anti-proliferative activity and inhibition of protein kinase activity⁽⁷⁰⁾. Soya has been hypothesised to reduce BC risk by shifting oestrogen metabolites that are genotoxic towards other inactive forms^(63,66). Soya is also known to have anti-proliferative, pro-apoptotic, antiangiogenic, antioxidative and anti-inflammatory effects⁽¹³⁾.

Study strengths and limitations

We evaluated the association of BC with four vegetarian dietary patterns representing a wide range of dietary habits. This and the relatively large number of vegans provide unusual (but for vegans at this time still relatively low) statistical power to test these hypotheses. Other advantages include the large number of Black participants and the reduced potential for confounding

because of this population's abstinence from, or very low use of, alcohol and tobacco.

However, this is an observational study that inevitably contains errors in the dietary data, although in this population dietary patterns can probably be assigned with relatively good validity. Another limitation is the low meat consumption of the reference group (on average about 54 g/d) that may cause an underestimation of the effect of a vegetarian diet as compared with a more typical non-vegetarian diet.

Finally, confounding is always a possibility despite adjustment for known correlates of vegetarianism and BC. Although we adjusted for screening (mammography), which had a borderline significant association with higher rates, residual confounding is possible. Two sensitivity analyses were performed to evaluate this possibility. First, when the screening variable was removed from the model, the association with vegans changed only from 0.77 to 0.74. Second, it is possible that vegans may have delayed their ages at cancer diagnosis because of their lower screening rates. Thus, for this sensitivity analysis, 1 year was subtracted from the age at censoring (for any cause) in all subjects who did not screen according to recommendations. This brought forward the age at diagnosis of BC in these subjects, and also eliminated observations in the year before censoring for other causes (when there could have been a missed early BC because of lack of screening). Next, the association with vegans again only changes from 0.77 to 0.76. Thus, this suggests that any residual confounding from this source is likely to be minor.

Conclusions

In conclusion, participants in this cohort who follow a vegetarian dietary pattern overall did not experience a lower risk of BC as compared with non-vegetarians. However, those adhering to a vegan dietary pattern showed consistently lower point estimates in various subgroups but these were not statistically significant. Numbers of cancers in vegans were relatively small, and these analyses should be repeated in the AHS-2 cohort after a longer follow-up to determine whether the same trends continue when power is greater.

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Registry', 'Massachusetts Cancer Registry', 'Michigan Cancer Surveillance System', 'Minnesota Cancer Surveillance System', 'Mississippi Cancer Registry', 'Missouri Cancer Registry and Research Center', 'Montana Central Tumor Registry', 'Nebraska Cancer Registry', 'Nevada Central Cancer Registry', 'New Hampshire State Cancer Registry', 'New Jersey State Cancer Registry', 'New Mexico Tumor Registry', 'New York State Cancer Registry', 'North Carolina Central Cancer Registry', 'North Dakota Statewide Cancer Registry', 'Ohio Cancer Incidence Surveillance System', 'Oklahoma Central Cancer Registry', 'Oregon State Cancer Registry', 'Pennsylvania Cancer Registry', 'Rhode Island Cancer Registry', 'South Carolina Central Cancer Registry', 'South Dakota Cancer Registry', 'Tennessee Cancer Registry', 'Texas Cancer Registry', 'Utah Cancer Registry, NCI Contract HHSN261201300071', 'Vermont Cancer Registry', 'Virginia Cancer Registry', 'Washington State Cancer Registry', 'West Virginia Cancer Registry', 'Wyoming Cancer Surveillance Program'. The results reported here and the conclusions based on them are the sole responsibility of the authors.

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G. E. F., S. K., L. B. and K. J.-S. formulated the research question. G. E. F. and J. A. P.-S. designed the study. G. E. F., P. H., K. J.-S., L. B. and S. K. carried it out. J. A. P.-S. and J. F. analysed the data. J. A. P.-S. and G. E. F. wrote the manuscript. All authors critically reviewed the manuscript.

The authors declare that there are no conflicts of interest.

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